(19) **RU** (11) **2140291** (13) **C1**

(51) 6 A61K47/44, A61K47/26, A61K47/14, A61K9/48

(12) SPECIFICATION OF THE INVENTION TO RF PATENT

Status: as of 25 July 2008 - operates

(21) Application **96102012/14**

(22) Filing application date **1994.07.08**

(24) Date of beginning of the term of validity of the patent **1994.07.08**

(31) Number of conventional application: **P 43 22 826.7**

(33) Country **DE**

(45) Published **1999.10.27**

(45) List of documents cited in the search report: 1. **RU 2053764 C1, 10.02.96. GB 2228198 A, 22.08.90. 3. GB 2257359 A, 13.01.93. 4. EP 0327280 A1, 09.08.89. 5. EP 0448091 A2, 25.19.91.**

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(85) Date of correspondence with art. 22/39 PCT: **08.02.96**

(86) Number and date of international or regional application: **EP 94/02238 (08.07.94)**

(87) Number and date of international or regional application: **WO 95/01785 (19.01.95)**

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(54) A pharmaceutical composition for solubilization of a poorly soluble active agent in a composition carrier and a method for the preparation thereof.

The invention relates to the field of pharmacy. A pharmaceutical composition of

acid sorbitan esters as solubilizing agents in the combination with lipophilic excipients and nonionic surface active and nonionic surface active substances. The composition is obtained by mixing carrier components followed by dispersing the poorly soluble agent. The obtained composition exhibits the enhanced biological availability at oral administration. 2 independent and 11 dependent claims.

THE SPECIFICATION OF THE INVENTION

The subject matter of this invention is pharmaceutical compositions for poorly soluble agents as well as methods of making these compositions.

Generally, the oral administration of a pharmaceutical active agent, for example in the form of tablets, capsules and dragees, has a number of advantages as compared with other, for example parenteral, forms of administration. Subjectively, diseases, the treatment of which should be carried out by injections, are considered as more serious as compared with other diseases, in the case of which taking of tablets, capsules or drugs is recommended. The most essential advantage is convenience of such forms for the administration by a patient itself, while parenteral administration should be carried out most every by a doctor or qualified nurse.

After administration and decomposition of an orally administered form, a liquid in the gastrointestinal tract, for example gastric or intestinal juice, has an effect on the active agent. Many active agents for oral administration have lipophilic properties and are therefore poor soluble in the aqueous environment of the gastrointestinal tract. Under these circumstances, the amount of the active agent, which is possible to intake, is reduced; therefore, the biological availability thereof is reduced. As a rule, it is unavoidable results in the increase of introduced dosages of the active agents. The consequences of this are the increased biological changeability and undesirable variations in efficacy.

In order to improve the solubility of the poorly soluble active agents, so-called solubilizing agents as, for example, hydrophilic co-solvents such as ethanol, propylene glycol, liquid polyethylene glycols, or lipophilic solubilizing agents such as lecithin, fatty acid polyglycol esters or fatty acid glycine-polyglycol esters

were described. There are problems upon the use of such solubilizing agents due to the reduced tolerance and inadequate stability of the form for administration, for example separation effects.

Therefore [1], the Examiner has proposed the use of partial fatty acid glycerol esters or partial polypropylene glycol esters. Such excipients (co-surfactants) are low suitable, since they are available only in the narrow HLB range from 2 to 3. This makes it possible only insignificant change in proportions of components of the composition carrier with the aim of adaptation to different solubilities of the active agents, which should be subjected to the solubilization.

The aim of the instant invention is the increase or reduce of solubility, resorbtion capacity and, consequently, a biological availability of the active agents for oral administration by selection of more suitable excipients.

This aim is resolved in the instant invention, in accordance with which invention the improved pharmaceutical composition is proposed in order to increase the solubility of the active agent having poor solubility in water, in the composition carrier. In accordance with this invention, the indicated composition carrier comprises the following components:

a) about 10-50% by weight, based on the carrier composition, of a co-surfactant which is substantially pure or which is in the form of a mixture, having a hydrophilic-lipophilic balance of less than 10 (HLB value according to Griffin), selected from the group consisting of polyglycerol fatty acid esters and sorbitan fatty acid esters;

b) about 5-40% by weight, based on the carrier composition, of a pharmaceutically acceptable oil which is substantially pure or which is in the form of a mixture, comprising a triglyceride as essential lipophilic component; and

c) about 10-50% by weight, based of the carrier composition, of a nonionic surfactant which is substantially pure or which is in the form of a mixture, having a HLB value of more than 10;

and further optional pharmaceutically acceptable excipients.

Furthermore, the subject of the invention is also a method for preparing a pharmaceutical composition, comprising a solubilizing active agent with poor solubility in water, in the composition carrier consisting of the indicated components. The indicated pharmaceutical composition is suitable for filling single dosage forms for oral administration, for example starch, solid gelatinous and soft gelatinous capsules.

The terms, used above and further, are determined in the following manner within the scope of the specification of the instant invention:

The term "pharmaceutical composition" is a mixture of the solubilised pharmaceutical active agent or a mixture of active agents having poor solubility in water with the indicated composition carrier consisting of the indicated components, wherein the indicated mixture can be processed to oral dosage forms, preferably starch, solid gelatinous and soft gelatinous capsules.

The term "solubilised" or "solubilization of an active agent or a mixture of active agents having poor solubility in water is a process of dispersion, which is realized through the action of a corresponding solubilizing agent, which increases the dispersion capacity of the active agent in such degree that a therapeutically effective dosage is completely dissolved or at least becomes available for biodegradation as a result of the process of partial dissolution. The term "dispersing capacity" is a measure of formation micro-emulsions, true molecular solutions of the active agents and excipients in water, as well colloidal solutions, for example solutions of associative colloids or molecular colloids, which may be clear or opalescent, and, if necessary, contain no solid particles at all after optional filtration, preferably wit sterile filters having a pore diameter of about 5-10 μm, or, for example, micellar solutions or spherocolloids which can only be separated by an ultracentrifuge. The dispersion capacity may be given in mg or mmole per liter of water.

A pharmaceutically active agent or a mixture of active agents, which are poor soluble in water, have a solubility in water of less than 500 mg/1000 ml, preferably of less than 200mg/1000 ml.

The most acceptable poorly soluble active agents are immunosuppressive agents having a macrolide structure, for example, cyclosporin A, cyclosporin G, rapamycin, tacrolimus, deoxyspergualin, mofetyl micophenolate, gusperimus; non-steroidal anti-inflammatory substances, in particular acetyl salicylic acid, ibuprofen or S(+)-ibuprofen, indomethacin, diclofenac, piroxicam, meloxicam, tenoxicam, naproxen, ketoprofen, flurbiprofen, phenoprofen, felbinac, sulindac, etodolac, oxyphenbutazone, nabumetone; dehydropyridine derivatives having cardiovascular activity, for example nifedipine, nitrendipine, nimodipine, nisoldipine, isradipine, felodipine, amlodipine, nilvadipine, lacidipine, benidipine, masnidipine, furnidipine, niguldipine; preparations for the treatment of diseases of nervous system, in particular α- lipoic acid, muramic peptides, in particular muramic dipeptides or tripeptides, romurtid, fat-soluble vitamins, in particular vitamins A, D, E or F; alkaloids, for example vincopectin, vincristine, vinblastine, reserpine, codein, ergot alkaloid, for example bromocriptine, dihydroergotamine, dihydroergocristine; antitumor drugs, for example chloroambucil, etoposide, teniposide, idoxifen, tallimustine, teloxantron, tirapazamine, carcelesine, dexniguldipine, intoplicine, idarubicine, miltefosine, trofostamide, teloxantrone, melphalane, lomustine, 4,5-bis-(4'-fluoroanilino)- phthalimide; 4,5-dianilinophthalimide; immunostimulants, for example timoctanane, copper acetate prezatide; anti-infectious substances, for example erythromycin, daunorubicin, gramicidin, doxorubicin, amphotericin B, gentamicin, leukomicin, streptomycin, ganephromicin, rifamexil, ramoplanin, spiramicin; antifungal agents, for example fluconazole, cetonazole, itraconazole; H2-receptor antagonists, for example famotidine, cimetidine, ranitidine, roxatidine, nisatidine, omeprazole, protein kinase inhibitors, for example N-[4-methyl-3-(4-pyridine-3-ylpyrimidine-2-ylamino)-phenyl]-benzamide, N-benzoyl-stausposporine; HIV-1-protease inhibitors, for example BOC-Phe^{c}Phe-Val-Phe-morpholine of O-[2-(2-methoxy-

cyclo-penthyl-oxycarbonyl-amino-1-methyl-indole-3-yl-methyl)-3-methoxy-benzoyl]-2-vinyloxy]-benzole-sulfonamide.

The most preferable agents are cyclosporins, rapamycin, tacrolimus, deoxyspergualin, mofetyl micophenolate, nifedipine, nimodipine, ethoposide, ibuprofen and α- lipoic acid.

Instead of an active agent, which is presented in the form of free acid or in the general form, the active agent may also be presented in the form of a pharmaceutically acceptable salt, for example in the form of hydrobromide, hydrochloride, mezilate, acetate, succinate, lactate, tartrat, fumarate, sulphate, maleate, etc, in the pharmaceutical composition.

A concentration of the active agent or the combination of active agents is determined in respect to a dose, which should be used. It may be in the range from 1 to 30% by weight, preferably from 5 to 20% by weight, especially from 5 to 12% by weight, based on the weight of the composition carrier.

The composition carrier for one of the listed active agents or for the combination of active agents is determined by the following manner.

The requirement "substantially pure" in respect to component, which is presented in the composition carrier, determines a degree of purity of this component as exceeding 90%, preferably more than 95%, before mixing with other components in the composition carrier. The component determined as "substantially pure" preferably has easily defined structure and makeup.

The components presented in the form of the mixture in the composition carrier may represent mixtures of natural agents, the makeup of which is provided by a raw stock itself, extraction and further treatment thereof.

The components of such mixtures should be presented in specifications attached by the Manufacturer.

Fatty acid polyglycerol ester of the component a) comprises an substantially pure fatty acid polyglycerol ester or a mixture of fatty acid polyglycerol esters, wherein polyglycerol comprises preferably up to 10 glycerol units inclusive, which are esterified, with 1-10 acid radicals of saturated or unsaturated carboxylic acids having an even number of 8-20 carbon atoms

An acid radical of the saturated carboxylic acid having an even number of 8-20 carbon atoms, which esterifies polyglycerol, preferably is an unbranched chain having 12, 14, 16 and 18 carbon atoms, for example n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl.

An acid radical of the unsaturated carboxylic acid having an even number of 8-20 carbon atoms, which esterifies polyglycerol, preferably is an unbranched chain having 12, 14, 16 and 18 carbon atoms, and a 1 double bound, for example 9-cis-dodecanoyl, 9-cis-tetradecenoyl, 9-cishexadecenoyl or 9-cis-octadecenoyl.

The names presented in parentheses are also conventional for the indicated radicals.

Furthermore, the following names are generally known for the indicated acid radicals: 9-cis-dodecenoyl (lauroleoyl), 9-cis-tetradecenoyl (miristoleyl), 9-cis-hexadecenoyl (palmitoleyl), 6-cis-octadecenoyl (petroseloyl), 6-trans-octadecenoyl (petroselaidoyl), 9-cis-octadecenoyl (oleyl), 9-trans-octadecenoyl (elaidoyl), 11-cis-octadecenoyl (vacenoyl), 9-cis-isocenoyl (hadoleoyl), n-dodecanoyl (lauroyl), n-tetradecanoyl (miristoyl), n-hexadecanoyl (palmitoyl) or n-octadecanoyl (stearoyl), n-isozanoyl (arachidoyl).

The acceptable fatty acid polyglycerol esters having easily defined structure are, for example (with English names) diglycerol monocaprate, diglycerol monopaurate, diglycerol diiosstearate, diglycerolmonoisostarate, diglyceroltetrastearate (polyglycerol-2-tetrastearate), triglycerol monooleate (polyglycerol-3-stearate), triglycerol monolaurate, triglycerol monostearate (decasolyglycerol-3-stearate), triglycerol monoisostearate, hexaglycerol dioleolate (polyglycerol-6-dioleate) hexaglycerol stearate (polyglycerol-6-distearate).

decaglycerol dioleate (polyglycerine-10-dioleate), decaglycerol tetraoleate (polyglycerol-10-tetraoleate), decaglycerol decaoleate (polyglycerol-10-decaoleate), decaglycerol decastearate (polyglycerol-10-decastearate). CFTA nomenclature is presented in brackets. These products are made under trade marks Caprol® (trade marks of company Karlshamns USA Inc., Columbus, Ohio). Specific product names: CAPROL 2G4S, 3GO, 3GS, 6G2O, 6G2S, 10G2O, 10G4O, 10G10O, 10G10S. Other products are produced under names DGLC-MC, DGLC-ML, DGLC-DISOS, DGLC-MISOS, TGLC-ML AND TGLC-MISOS by company Solvay Alkali GmbH, D-3002 Hannover.

A mixture of fatty acid polyglycerol esters is named as decaglycerol mono-, dioleate, mixed fatty acid polyglycerol ester, fatty acid polyglycerol ester, polyglycerol caprate, cocoat, laurate, lanoliate, isostearate or ricinolate and is produced under trade marks Triodan® and Homodan® (trade marks of company Grinsted Products, Grinsted Denmark), The exact names of the product TRIODAN 20, 55, r90 and HOMODAN MO, Radiamulus®. The trade marks of company Petrofina (FINA), Brussels, Belgium, the exact name of the product RADIAMULUS Poly 2253, under the name CAPROL PGE 860 or ET, or trade marks Plurol® (trade marks of Gattefosse Etablissements, SaintPriest, France, specific product names PLUROL Stearique WL 1009 or PLUROL Oleique WL 1173. These products are produced under names PGLC-C 1010 S, PGLC-C 810, OHLC-C 1010/S, PGLC-LT 2010, POLC-LAN 0510/S, PGLC-CT 2010/90, PGL-ISOS T UE, PGLC UE, OGLC0ISOS O410 by company Solvay Alkali GmbH, D-3002 Hannover.

The listed fatty acid polyglycerol esters satisfy the conditions [2]. The specifications of the products published by the listed manufacturers are the most appropriate with characteristics according to tables of data in respect to the corresponding product, especially such characteristics as the content of monoester, drop-incidence point, a free glycerin, a free fatty acid, iodine number, a form, antioxidants, a HLB value, properties and storage time.

In particular, the fatty acid polyglycerol esters satisfy the requirements [3], as well as [4].

A fatty acid sorbitan ester of the component a) preferably comprises substantially pure fatty acid sorbitan ester or a mixture of different fatty acid sorbitan esters, wherein sorbitan is esterified with 1-3 acid radicals of a saturated or unsaturated carboxylic acid with normal (unbranched) chain having an even number of 8-20 carbon atoms.

An acid radical of the saturated carboxylic acid having an even number of 8-20 carbon atoms, which esterifies sorbitan, preferably is normal with 12, 14, 16 and 18 carbon atoms, for example with n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl or n-octadecanoyl.

An acid radical of the unsaturated carboxylic acid having an even number of 8-20 carbon atoms, preferably is normal with 12, 14, 16 and 18 carbon atoms, for example oleoyl.

The suitable fatty acid sorbitan esters are, in particular, sorbitan monolaurate, - monopalmitate, - monostearate, -tristearate, - monooleate, -sesquioleate and – triolate. These products are industrially available under the trade marks Span® (trade marks of company Atlas, Wilmington, USA). Specific product names: SPAN 20, 40, 60, 65, 80 and 85, Arlacel® (trade marks of company Atlas), specific product names: ARLACEL 20, 40, 60, 65, 80, 85 and C, Crill® (trade marks of company Croda Chemicals Ltd., Cowick Hall, Snaith Goole, GB), specific product names: CRILL 1, 3 and 4, Dehymuls ® (trade marks of company Henkel, Desseldorf DE), specific product names: DEHYMULS SML, SMO, SMS, SSO, Famodan® (trade marks of company Grinsted Products, Grinsted Denmark), specific product names: FAMODAN MS and TS, Capmul® (trade marks of company Karlshamns USA Inc., Columbus, Ohio), specific product names CAPMUL S and O, Radiasurf® (trade marks of company Petrafina (FINA), Brussels, Belgium), specific product names: RADIASURF 7125, 7135, 7145 and 7155

The fatty acid sorbitan esters and fatty acid polyglycerol esters satisfy the requirements [5, 6]. The descriptions of the products published by the listed manufacturers are the most appropriate with characteristics according to data tables in respect to a corresponding product, especially such characteristics as a form, color, a HLB value, viscosity, increasing melting point and solubility.

The component a) has a HLB value, which does not exceed 10. It is presented in the composition carrier in an amount of 10 to 50% by weight, preferably 15-40% by weight, more preferably 15-20% by weight, based on the total weight of the composition carrier. The components a) may also comprise mixtures of fatty acid polyglycerol esters together or mixtures of sorbitan esters and fatty acids together, or mixtures of fatty acid polyglycerol esters with fatty acid sorbitan esters.

A pharmaceutically acceptable oil b) represents triglyceride of natural origin or synthetic or semi-synthetic substantially pure triglyceride. The preference is shown to triglyceride of natural origin, which is characterized in that glycerin is etherified by acid radicals of saturated or unsaturated carboxylic acids having an even number of 8-20 carbon atoms. Such acid radicals are listed earlier, for example n-dodecanoyl, n-tetradecanoyl, n-hexadecanoyl, n-octadecanoyl or oleoyl.

The suitable triglycerides of natural origin are, for example peanut oil, sesame oil, sunflower-seed oil, olive oil, corn oil, soyabean oil, castor oil, cottonseed oil, rapeseed oil, thistle oil, grape seed oil, fish oil or neutral oil.

The component b) is presented in the makeup of the composition carrier in an amount of about 5-40% by weight, preferably 10-35% be weight, on the basis of the total weight of the composition carrier. The components b) may consist of a mixture of the pharmaceutically acceptable oils.

A nonionic surface active agent c) with a HLB value of more than 10 preferable is an amphiphylic agent, a hydrophilic component of which consists of polyethylene oxide, wherein an average molecular weight of the component of polyethylene oxide is about 600-25000, which corresponds to 15060 units of ethylene oxide.

For example, products of the reaction of natural or hydrogenated castor oil and ethylene oxide are suitable nonionic surface active agents. These products are produced in a commercial manner under trade marks Gremophor®, Niccol® and Emulgin®. Polyoxyethylene esters on the basis of fatty acid derivatives of sorbitol (polysorbates), for example POE-(20)-sorbitan monolaurate, POE-(20)-sorbitan monopalmitate, POE-(20)-sorbitan tantristearate, POE-(20)-sorbitan monooleate or POE-(20)-sorbitan trioleate, as well as fatty acid polyoxyethylene esters, for example POE-(20, 30, 40, 50)-stearate, are also suitable nonionic surface active agents. These products are produced under the trade marks Tween® and Myrj®.

The component c) is presented in the composition carrier in an amount of about 10-50% by weight, preferably 20-25% by weight, based on the total weight of the composition carrier. The component c) may also consist of mixtures of the pharmaceutically acceptable nonionic surface active agents.

The suitable pharmaceutically acceptable additional excipients, as well as an active agent or the combination of active agents, are added into the composition carrier in such an amount that they consist up to 100% by weight with the components a), b) and c). The additional excipients may be presented in the composition carrier in amounts from 0% to about 75% by weight. The additional excipients are stipulated by the choice of a pharmaceutical ready form. Such pharmaceutically acceptable solutions as ethanol, propanol, isopropanol, propylene glycol, polyethylene glycol, glycerin or water, or mixtures thereof are added to liquid ready forms such as drops, suspensions or capsular fillers.

Furthermore, the usual excipients may be added, for example such preservatives as benzyl alcohol, ethanol, a n-hydroxybenzoic acid ester, sorbitol acid, antioxidants, for example tocopherols, butylhydroxy-anisole, benzylhydroxy-toluol, ascorbic acid, ascorbilpalmitate; stabilizers, in particular citric acid, tartaric acid, EDTA, aromatizing and aromatic agents.

Agents with the ordinary consistence are acceptable as capsular fillers of gelatinous capsules or plasticizers for the obtainment of a stable gelatinous

hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose, methylcellulose or a colloidal silicone dioxide are such excipients.

The following aspect of this invention is a method for the preparation of the pharmaceutical composition described above, characterized in that components a), b) and c) and possibly other pharmaceutically acceptable excipients are mixed together in any order, and the indicated pharmaceutically active agent, which is poor soluble in water, is dispersed in this mixture, and, if advisable, the dispersion system is transferred into the corresponding form for oral administration. Dispersing the active agent or mixture of active agents may be conducted after mixing the components a), b) and c), as well as the other excipients.

The dispersion of the active agent or composition of active agents may be conducted after mixing the components a), b) and c), as well as other excipients.

From the other side, the indicated active agent or the mixture of active agents may be in a separate component or in the mixture of two of the indicated components, and the remaining components are added after this. Solubilizing processes of dispersing may be accelerated by heating some components or a mixture thereof. Reaction conditions, which stimulate the formation of a colloidal dispersion phase, are preferable.

In the presence of active agents susceptible to oxygen, the process is conducted in an atmosphere of protective gas, for example under nitrogen, helium or argon. Oxygen, which is already contained in liquid components, may be eliminated by the creation of lower pressure about 50-100mbar, or by the treatment by ultrasound. A reaction container with double walls and stirrer is suitable for the conduction of the process.

The transfer into the form suitable for oral administration is carried out by the known method. Processes known from the prior art [7, 8] are used for the preparation of the liquid forms for oral administration such as drops, suspensions, emulsions, etc.

Double gelatinous capsules, which may be obtained by adding glycerin or sorbitol and quickly enough dissolve under the action of gastric juices, are preferable from capsules. Furthermore, starch capsules may be used, for example commercial samples made under trade mark Capill® by company Capsugel/Warner Lambert. Other excipients and fillers such as lactose, starch, lubricants such as amylum or magnesium stearate, may be mixed with capsules. The soft capsules may additionally comprise such liquids as lecithin, fats, oils, paraffinic oil or a liquid polyethylene glycol. The double capsules having sizes 0-4, preferably 0-2, are used in dependence upon the dose. The commercial products of companies Shionogi, Capsugel or Scherer are used.

The following examples illustrate the invention without limiting the general scope thereof, described above. Active agents are representatives of all of the groups of active agents mentioned earlier. Temperatures are given in centigrade degrees.

Example 1

A method of filling into soft gelatinous capsules. Amounts are given in mg per filled capsule, size of soft gelatinous capsules: 22 minims, oblong.

1. Cyclosporin A (USP XXII/Pharm.Eur.)-100.0
2. POE-(40)-hydrogenated castor oil (CREMOPHOR RH 40, NICCOL HCO 40, SIMULSOL 1293) – 400.0.
3. Fatty acid di/tri/tetraglycerol ester (FCC/TRIODAN 20) – 238.0
4. Sesame oil (DAB 10) – 160.0
5. Alpha-tocopherol (DAB 10) – 2.0
6. Ethanol (DAB 10) – 100.0

Components 2-4 are mixed in a stainless steel vessel equipped with stirrer, while heating to 40°. The solution is then degassed by applying low pressure. Antioxidant 5 is added to the clear solution, and the therapeutic agent cyclosporin A is then dispersed therein. After addition of the ethanol, the entire composition is stirred until a clear solution is obtained. This solution is cooled to 20^0C and then filled into soft gelatin capsules. To compensate for evaporation, the amount of ethanol added is 30-60 mg higher than in the above composition.

In addition to gelatin, the shells of the soft gelatin capsules contain excipients, which influence the consistency, typically glycerol and/or propylene glycol, or sorbitol and/or mannitol. The shells can additionally contain pigments or colourants, typically titanium dioxide, iron oxide, quinoline yellow, or cochenille red A.

Example 2

A method of filling into solid gelatinous capsules or starch capsules. Amounts are given in kg per portion.

1. Nifedipine (DAB 10) – 20.0
2. POE-(20)-sorbitan monooleate (polysorbate 20 Pharm. Eur., TWIN 20) – 168.0
3. Triglycerol mono/dioleate (FCC-CAPROL 3GO) – 28.0
4. Neutral oil (MIGLYOL 812, CAPTEX 300/400)- 84.0

All components of the composition are mixed at 45^0C in a double-walled heating vessel having a volume of 300 liters and are stirred until a clear solution is obtained. 300 mg each of the cooled clear solution are filled into hard gelatin capsules of size 1 made opaque with titanium dioxide/iron oxide.

The filled capsules are banded. Owing to the susceptibility of nifedipine to light, all process steps must be carried out excluding daylight.

Example 3

A method of filling unto glass bottles. The composition is suitable for oral administration in the form of drop solution filled in a brown small bottle with a dropping bottle having capacity of 40 ml. Amounts are given in grammes.

1. Nimodipine – 3.0
2. POE-(60)- hydrogenated castor oil (CREMOPHOR RH 60, NICCOL HCO 60, SIMULSOL 1294) – 15.0.
3. Sorbitan monolaurate (BPC 1973, SPAN 20) – 8.5
4. Sunflower-seed oil (DAP 10) – 8.5
5. Propylene glycol – 5.0

The solution is prepared in general accordance with the procedure of Example 2.

Example 4

A method of filling into soft gelatinous capsules. Amounts are given in mg per filler capsule. Size of gelatinous capsule: 4 minims, oblong.

1. Tacrolimus – 10.0
2. POE-(35)-castor oil (CREMOPHOR EL) – 72.0
3. Sorbitan monolaurate (SPAN 80) – 72.0
4. Neutral oil – 32.0
5. Alpha-tocopherol – 1.0
6. Polypropylene glycol (DAB 10) – 5.0

The capsules are prepared in general accordance with the procedure of Example 1. Propylene glycol is particularly suitable as plasticiser for the capsule shell.

Example 5

A method of filling into solid gelatinous capsules. Amounts relate to the filling of one size 0 capsule.

1. Alpha-lipoic acid – 100.0
2. POE-(40)-stearate (US/NF, MYRJ 52 S) – 80.0
3. Tetraglycol stearate (FCC, TRIODAN 55) – 215.0
4. Sesame oil – 160.0
5. Butylhydrooxyanisole – 0.5

The solution is prepared in general accordance with the procedure of Example 2, additionally observing the susceptibility of the liponic acid to oxygen.

Example 6

A method of filling into soft gelatinous capsules. Amounts are given in mg per filler capsule. Size of the soft gelatinous capsule: 6 minims, oblong.

1. Rapamicine – 20.0
2. POLYSORBATE 80 (Twin 80) – 150.0
3. Sorbitan monooleate – 25.0
4. Neutral oil – 75.0
5. Ascorbyl palmitate – 0.5
6. Benzyl alcohol (DAB 10) – 5.0

The composition is prepared in general accordance with the procedure of Example

Example 7

A method of filling into soft gelatinous capsules. Amounts are given in mg per filler capsule.

1. Ethoposide – 100.0
2. POE-(40)- hydrogenated castor oil – 400.0
3. Di-/tri-/tetraglycerol laurate (TGCL-laurate T2010 Solvay Alkali GmbH) – 160.0
4. Sesame oil – 230.0
5. Ethanol – 100.0

The solution is prepared in general accordance with the procedure of Example 2.

Example 8

A method of filling into soft gelatinous capsules. Amounts are given in mg per filler capsule. Size of soft gelatinous capsule: 9.5 minims, oblong.

1. S(+)-ibuprofen – 100.0
2. POLYSORBATE 60 (Twin 60) – 210.0
3. Hexaglycerol dioleate (CAPROL 6G20) – 130.0
4. Castor oil (DAB 10) – 60.0

The composition is prepared in general accordance with the procedure of Example 1.

Cited documents

1. The specification of German DOS 40 05 190.
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4. U.S. FDA Code 21 CFR 172.854
5. British Pharmacopeia (special monograph).
6. Ph. Helv. VI.
7. Hagers Handbuch der Phrmazeutishen Praxis.
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1. A pharmaceutical composition comprising a poorly soluble active agent and a composition carrier for the solubilisation thereof, characterized in that the composition carrier comprises the following components:

a) 10-50% by weight, based on the total weight of the carrier composition, of a co-surfactant which is substantially pure or which is in the form of a mixture, having a hydrophilic-lipophilic balance of less than 10 (HLB value according to Griffin), selected from the group consisting of polyglycerol fatty acid esters and sorbitan fatty acid esters;

b) 5-40% by weight, based on the total weight of the carrier composition, of a pharmaceutically acceptable oil which is substantially pure or which is in the form of a mixture, comprising a triglyceride as essential lipophilic component; and

c) 10-50% by weight, based of the total weight of the carrier composition, of a nonionic surfactant which is substantially pure or which is in the form of a mixture, having a HLB value of more than 10;

and further optional pharmaceutically acceptable excipients.

2. A pharmaceutical composition according to claim 1, characterized in that it additionally comprises other pharmaceutically acceptable excipients.

3. A pharmaceutical composition according to claim 1, characterized in that it comprises 1-30% by weight, based on the total weight of the carrier composition, of a poor soluble active agent having a solubility in pure water of less than 500 mg/1000 ml, wherein the agent selected from the group consisting of cyclosporin, rapamycin, tacrolimus, deoxyspergualin, micophenolate mofetil, nifedipine, nimodipine, etoposide, ibuprofen or α-lipoic acid is used as the poor soluble agent.

4. A pharmaceutical composition according to any one of claims 1 - 3, characterized in that said active agent is cyclosporin A.

5. A pharmaceutical composition according to any one of claims 1-4, characterized in that the composition carrier as component a) contains a substantially pure fatty acid polyglycerol ester or a mixture of such esters, wherein polyglycerol contains up to and including 10 units of glycerol which

are esterified with 1-10 acid radicals of saturated or unsaturated carboxylic acids having an even number of 8-20 carbon atoms.

6. A pharmaceutical composition according to claim 5, characterized in that component a) contains as fatty acid polyglycerol ester substantially pure polyglyceryl 2-tetrastearate, polyglyceryl -3-monooleate, polyglyceryl -3-stearate, polyglyceryl -6-dioleate, polyglyceryl -6-distearate, polyglyceryl-10-dioleate, polyglyceryl -10-tetraoleate, polyglyceryl -10-decaoleate or polyglyceryl-10-decastearate, or mixtures thereof.

7. A pharmaceutical composition according to any one of claims 1 - 4, characterized in that component a) comprises a substantially pure fatty acid sorbitan ester, or a mixture of fatty acid sorbitan esters, wherein the sorbitan is esterified with 1-3 acid radicals of saturated or unsaturated carboxylic acids having an even number of 8-20 carboxylic atoms.

8. A pharmaceutical composition according to claim 7, characterized in that component a) contains as fatty acid sorbitan ester substantially pure sorbitan monolaurate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, sorbitan monooleate, sorbitan sesquioleate or sorbitan trioleate, or mixtures thereof.

9. A pharmaceutical composition according to any one of claims 1-8, characterized in that component b) contains as pharmaceutically acceptable oil ground nut oil, sesame oil, sunflower oil, olive oil, corn oil, soybean oil, castor oil, cottonseed oil, rape-seed oil, thistle oil, grape-seed oil, fish oil or neutral oil, and component c) contains a nonionic surfactant with a hydrophilic component consisting of 15-60 units of ethylene oxide.

10. A process for the preparation of a pharmaceutical composition according to claim 1, which comprises mixing components a), b) and c) in any order, [illegible] this mixture the poor soluble agent

11. A process according to claim 10, wherein further optional pharmaceutically acceptable water-soluble excipients are introduced into the mixture.

12. A process according to claim 10, which comprises processing the obtained dispersion to a suitable dosage form for oral administration.

13. A proves according to claim 12, which comprises filling the dispersion into starch or hard or soft gelatinous capsules.

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Знаков с пробелами - 35023

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